UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,913	10/20/2003	**Rudolf Wank**	104341.B090019	2270

23911 7590 03/03/2010

CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
03/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,913	WANK, RUDOLF	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-7-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed December 7, 2009 are acknowledged.

   Claim 29 has been amended.

   Claims 29-34 are pending.

   The previous grounds of rejection can be found in the Office Action mailed August 7, 2009.

Withdrawn Rejections

2. The previous rejection under 35 USC 112, 2nd paragraph has been withdrawn in view of applicant's amendment to claim 29.

3. The previous rejections under 35 U.S.C. § 103(a) have been withdrawn upon further consideration and in view of applicant's arguments. In particular, these rejections have been withdrawn primarily because the method of Sekine is solely focused on preparing tumor reactive immune cells from a starting population of peripheral blood *lymphocytes* in a monocyte independent manner (see applicant's argument at pages 5-7, including page 7, 2nd paragraph). In contrast, the claimed method requires as its first step "stimulating peripheral-blood *mononuclear cells* (PBMC) with immobilized anti-CD3…" and is thus performed with not only lymphocytes but also monocytes (see the instant specification at Section 2 bridging pages 9-10 and at page 14, 1st paragraph). Furthermore, applicant's argument that "CAPRI" cells surprisingly provoke MHC class I and II expression by tumor cells while anti-CD3 activated PBMC do not (see paragraph bridging pages 10-11 of applicant's remarks as well as page 6, 1st paragraph and Figure 3 of the manuscript of Wank et al., submitted as Exhibit A with applicant's remarks) is also found convincing.

4. Moreover, the previous rejection under 35 U.S.C. 102(e) has been withdrawn upon further consideration but *not* in view of applicant's argument. In particular, to be clear applicant's argument that Gruenberg is not valid prior art under 35 U.S.C. 102(e) because the earliest priority date of Gruenberg is predated by the filing date of DE 101 20 505.8 to which the instant application claims the benefit of priority is *not* found convincing because applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. While the claim to the benefit of priority of the filing date of DE 101 20 505.8 put forth in this application is valid, the examiner cannot establish that the priority document satisfies the enablement and description requirements of 35 U.S.C. 112, first paragraph with respect to the claimed invention in the absence of an English language translation of said priority document.

   A New Grounds of Rejection is put forth below.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 29-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Michael Gruenberg (US 2003/0175272 A1)) in view of Gold et al. (J Surg Res. 1995 Aug;59(2):279-86).

Gruenberg teaches a method for treating cancer comprising stimulating T-cells with immobilized anti-CD3 then restimulating said T cells with a second addition of naïve PBMC followed by intravenous administration to the cancer patient (see, e.g., page 1, paragraph [0011]; page 2, paragraphs [0014]-[0015] and [0025]; page 3, paragraph [0033]; page 5, paragraph [0060]; page 7, paragraph [0089]; page 10, Example 4; and claim 5).

Gruenberg differs from the claimed invention in not explicitly teaching that the T-cells stimulated in the first step of their method could be T cells contained within a population of peripheral blood mononuclear cells (PBMC).

However, Gold teaches antigen-specific secondary responses can be recalled ex vivo by anti-CD3 antibody nonspecific activation of PBMC isolated from a cancer patient, even in the absence of specific antigen. Gold further teaches that the major cells activated in this approach are CD44+ memory T-cells, consistent with other reports of memory T-cell activation ex vivo without the requirement for antigen to be present in the culture system. "Therefore, it appears that nonspecific ex vivo activation of lymphocytes from murine and human [tumor-bearing hosts] is capable of generating specific anti-tumor effectors." Lastly, Gold teaches that PBMC isolated from a cancer patient and activated nonspecifically with anti-CD3 antibody can be used to effectively treat melanoma. (see, in particular, paragraph bridging pages 279-280; page 284 column bridging paragraph to right column, 1st paragraph).

Given the reference teachings it would have been obvious to one of ordinary skill in the art that the method of Gruenberg could be modified by the substitution of peripheral blood mononuclear cells as the starting source material to be stimulated with immobilized anti-CD3 antibody rather than T lymphocytes, and further that cells prepared in this way could be used to treat melanoma consistent with eth teachings of Gold.

One of ordinary skill in the art would have had a reasonable expectation of success in making such a substitution in light of the teachings of Gold that antigen-specific secondary responses can be recalled ex vivo by anti-CD3 antibody nonspecific activation of PBMC isolated from a cancer patient, even in the absence of specific antigen. Moreover, one of ordinary skill in the art would have been motivated to make such a substitution because it simplifies the

method of treatment by eliminating a purification step for the source material to be stimulated with immobilized anti-CD3 antibody.

Furthermore, since incubation of PBMC with anti-CD3 was known to produce interferon-γ as taught by Gold, one of ordinary skill in the art in practicing the teachings of Gruenberg in view of Gold would necessarily be meeting this limitation of claim 29.

A difference with respect to the teachings of Gold and the claimed invention is that according to Gold the method of making autologous activated lymphocytes for treating cancer involves an intermediate step of harvesting the cell culture supernatant produced during exposure of a first population of PBMC to anti-CD3 (referred to as "T3CS" cell culture supernatant by Gold), before adding it to a second population of PBMC cells obtained from a cancer patient resulting in their stimulation.

However, given the teachings of Gold, a person ordinary skill in the art applying ordinary creativity, common sense and logic would have immediately appreciated that, while perhaps less amenable to large scale use, it would not be unreasonable to drop the step of generating aliquots of T3CS cell culture supernatant in advance and instead simply (a) obtain PBMC from a patient and (b) expose said PBMC to anti-CD3 to make the activated PBMC of Gold and (c) substitute this activated PBMC of Gold for the T lymphocyte source material of Gruenberg.

As to using CAPRI cells in a dosage range from 0.5 to 30 million cells, Gold teaches the use of "small numbers (10^6)" of anti-CD3 ex vivo activated PBMC for treating murine carcinoma in conjunction with surgical treatment.

Moreover, Gold further teaches that previous studies demonstrated a benefit of using 10^7 cells, the difference being the previous treatment used cell therapy alone (see page 284 column bridging paragraph). According to Gold the success of lower dose cell therapy in conjunction with a another therapeutic treatment was also seen in a study demonstrating successful treatment with sub-therapeutic tumor infiltrating lymphocytes + cyclophosphamide. As is well known to one of ordinary skill in the art like surgical excision and cyclophosphamide radiotherapy is yet another common means of treating cancer.

Thus, while none of the cited references explicitly teach administration of autologous activated lymphocytes in conjunction with radiotherapy, it would have been prima facie obvious for one of ordinary skill in the art to do so given that each of these therapeutic treatments is known in the art to be useful for same purpose, the idea of combining them flowing logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Furthermore, one of ordinary skill in the art would have been motivated to combine the administration of activated PBMC according to the reference teachings with radiotherapy given that it is well known to one of ordinary skill in the art to expect a "synergistic" effect

of therapeutic agents when said agents (1) have a common utility, i.e., treating cancer, and (2) have distinct reaction mechanisms, i.e., killing dividing cells with radiant energy and killing cells by immune cell-based mechanisms. Furthermore, one of ordinary skill in the art would have been motivated to do so because, as is well known to one of ordinary skill in the art, synergistic effects often allow for dose reduction of the individual components yielding lower toxicity. Furthermore, one of ordinary skill in the art also readily understands that there are many market pressures to reduce dosing while maintaining treatment efficacy such as reducing the cost of manufacturing.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Michael Gruenberg (US 2003/0175272 A1)) in view of Gold et al. (J Surg Res. 1995 Aug;59(2):279-86) as applied to claims 29-32 and 34 above, and further in view of Gale Granger (5,837,233, of record) and Johnson et al. (5,217,704, of record).

The teaching of Gruenberg and Gold are given above.

Gruenberg and Gold do not explicitly teach administration of activated PBMCs directly into the tumor of the patient when the tumor is less than 0.5 cm.

However, Granger teaches a method of treating various human tumors comprising incubating PBMCs obtained from the cancer patient with allogeneic donor PBMCs ex vivo and then administering the cells directly into the tumor. (see, in particular, columns 10-11 and Examples 1-3). Granger further teaches that cytokine production directly within a tumor can induce tumor regression and that intralesional administration of immunotherapy is considered to be safer than systemic administration (see, in particular columns 1-3).

Moreover, Johnson teaches that "imaging of small, malignant lesions in a human subject in order to treat or cure the malignancy is a prime objective in current cancer treatment. If a malignant lesion or tumor can be detected at a very early stage, treatment through surgery, chemotherapy, radiation or other methods can be performed…the present invention images small malignant lesions with tumor masses from about 0.5 cm in diameter." (see, in particular, column 27, 2nd paragraph).

Thus, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Gruenberg and Gold directly into a small tumor, such as tumor of about 0.5 cm. In particular, given that it is easier to treat a small tumor than a larger tumor as is well known by one of ordinary skill in the art and as is echoed by Johnson,

and further given that as taught by Granger intratumor administration of T cells expressing cytokines can induce tumor regression and has safety benefits over systemic administration, one of ordinary skill in the art would have been motivated to treat cancer by administering activated PBMCs generated according to the teachings of Gruenberg and Gold directly into a small tumor, such as tumor of about 0.5 cm.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644